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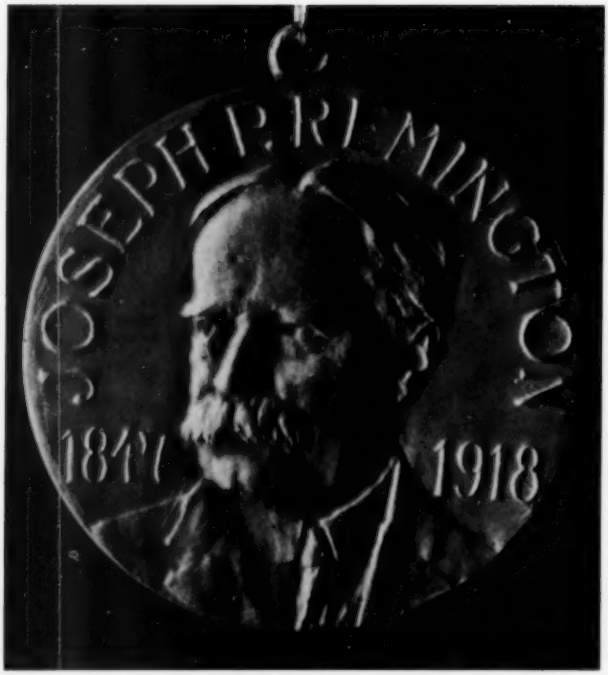

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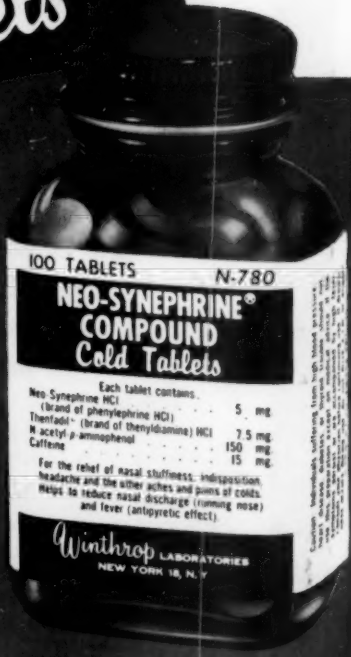

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E D I T O R I A L

AN UNWARRANTED ATTACK

IT is somewhat ironic that during 1958 the one industry in America that stands unequalled in the world, the drug industry, should be singled out for government criticism and attack while the real culprits and weaknesses on the American scene go almost unnoticed. In no industry is there more active competition, more energetic research, or more dramatic progress. The fate of those who fail to keep up with this ever increasing tempo is obsolescence, and a loss in sales and competitive position.

The philosophy behind the criticism of the drug industry is in keeping with the times for it has become good statesmanship in America to give the masses what is popular and what they want regardless of how wrong it is or how harmful to the country. It is this sort of political expediency and chicanery which keeps the national budget unbalanced in times of unprecedented prosperity, permits the most unbelievable excesses in certain corrupt labor unions, and fails to recognize our most serious national weaknesses such as in education and civil rights.

It is very good politics to criticize the drug industry since the average man is never happy about the outlay of a few dollars for drugs, even though it saves his life. The thousands he spends for a chrome bedecked and gadgeted monstrosity called an automobile, he spends gladly and even goes in debt willingly to obtain it. For such an overpriced luxury, his interest and carrying charges alone per year exceed his annual drug bill, but he gives this no thought at all. The same is true of his purchase of a television set even though its screen is so large that it cannot be properly viewed except in a room twice the size of that in which he can install it. Liquor and tobacco, each in its own right, consume more of the average man's income than do drugs. Since the government participates heavily in splitting the profit on liquor via alcohol taxes, this industry is beyond criticism and, although tobacco shortens life and contributes to many morbid diseases, it too is profitable and beyond reproach. Gambling is also a multi-million

dollar industry but it is opposed by government not on moral grounds but only when it fails to share in the proceeds.

The entire sales of the drug industry in the United States just about equals the gross profits of the General Motors Corporation but yet, because of its peculiar position of having no one really wanting to buy its products, our industry is particularly vulnerable to criticism.

The philosophy behind the American way of life is that private initiative with proper incentives will surpass an economy based on government ownership and control of the means of production. In no area of American industry has there been more dramatic evidence of the success of private initiative than in the field of drugs and medicines. The evidence is everywhere about us—the imposing array of new drugs, the tremendous growth of research and production facilities, the excellent pay rate of workers in the industry, and the market value of drug stocks.

There is nothing immoral or illegal about profit accruing to those whose vision, initiative, and energy have created new products for which there is a demand. This has been the case in the drug industry. It so happens, however, that for each product which is a success there are dozens of failures. All of these must have the cost of the research and effort underlying them covered by the profit on the single success, and these costs are sometimes staggering. It also happens, at times, that the patent situation on a new drug is so involved that no clear-cut ownership can be established. The only alternative is a cross-licensing arrangement so that two or more companies can participate in the market without costly litigation. Even so, the price of the drug invariably drops as the participants compete for the available market. Drug costs today consume less of expendable income than ever before in spite of the miracles that have been achieved through research.

It would seem to us that there are urgent areas requiring government attention and action far more than does our industry. If restraint of trade or unfair practices are the areas of government interest, these should not be hard to find. Many have been well publicized in the press and by Congressional Committees. If the Federal Trade Commission really wants to do something in connection with the drug industry, it might do a better job of policing the radio and television advertising of certain proprietaries sold to the public. This, however,

while needed, is not glamorous and headline-catching nor does it have public appeal.

In these times of serious challenge to our way of life, it would be well if we directed our attention to some of the critical areas now getting little or no attention. If indeed we lose our world position in the next few decades—and this is not an impossibility—it will not be American industry which is to blame but the lack of it. We need desperately those things which contribute to the strength of industry. Among these are competent, efficient and dedicated manpower. Such men are increasingly hard to find.

With all the emphasis on engineering engendered by Russia's successes, freshman engineering students in the United States dropped 11 per cent in 1958 and other scientific and professional fields are equally hard pressed for competent recruits. Science and engineering students can come only as a result of inspired and effective teaching at the elementary and secondary school level. In spite of this, no really effective national program has been forthcoming to improve public school teaching, nor will it until teachers again gain that public recognition, respect, and salary which is their due. Only this coupled with a public awareness that all is not well with our sense of values can change things as they must be changed. Young people are not likey to choose a life dedicated to study, science, and service while those who try to so motivate them earn less than garbage collectors. They are more impressed with the performance of "entertainers" who are public idols and are paid millions of dollars a year skillfully programmed by legal talent so that it is not taxed away. Neither does truth, justice, or hard work seem very promising when certain union leaders live in luxury, and with seeming success and immunity defy even the most basic laws of the land.

Yes, we have many things on the American scene which not only need attention but demand it. The drug industry, while it may not be perfect, is not one which deserves to be singled out and harassed. It is the envy of the world and no Soviet "medicinal Sputnik" has challenged it or is likely to. If reform in America is the order of the day, we should find several things of higher priority than the drug industry which deserve attention.

L. F. Tice

SURFACE ACTIVE AGENTS IN PARENTERALS *

A Review

By Walter F. Charnicki **

COUNTLESS numbers of surfactants have been synthesized and described in the last 10-20 years. In spite of this, however, only very few of such compounds are described as being useful in parenteral formulations. The bulk of the pharmaceutical use of surface active agents has been described for topical preparations. One reference entitled "Handbook of Cosmetic Materials" (1) contains 2,734 references, a great portion of which are devoted to surfactants. Unfortunately, no such review on their application in parenterals could be found. Limited toxicological data on the commercially available surfactants may be the major contributing factor to this paucity of information. Low concentrations of these compounds are capable of exerting profound pharmacodynamic effects. It is, therefore, essential that they be studied thoroughly for their toxicological properties in order to determine safe quantities and conditions for parenteral use.

Historically, compounds which display surface activity are by no means new. Soaps have been known since the early days of the Roman Empire and sulfonated oils are more than one hundred years old. In nature, surfactants appear as bile acids, the lecithins and glucosides particularly the saponins.

It is not the intent of this presentation to discuss the history of surface active agents, the chemistry or theories and principles which govern their behavior. This has already been done by Valko (2), Lawrence (3), Schwartz, Perry, and Berch (4) and others.

Instead, it is the purpose of this discussion to briefly review some of the applications of surface active agents in parenteral dosage forms.

Surface active agent is a general term applicable to a great variety of compounds and uses. These agents may be defined as substances

* Presented at the Annual Meeting of the Parenteral Drug Association in New York City, October 24, 1958.

** Merck Sharp & Dohme Research Division, Merck & Co., Inc., West Point, Pa. Present address: Smith Dorsey Co., Lincoln, Nebraska.

which alter the energy relationships at interfaces and, although this is correct, it may be too general for practical use. These are usually synthetic organic substances which in dilute solution are responsible for wetting, detergency, penetration, emulsification, foaming, solubilization, and dispersion. These are regarded as properties of the compounds. However, it should be pointed out that such "properties" are by no means simple but represent exceedingly complex phenomena involving the operation of a number of factors simultaneously. One must not overlook the fact that the properties mentioned above are closely interrelated and a surface active agent usually possesses all of these properties to some degree.

For example, a wetting agent is a substance that produces improved spreading qualities for a liquid on a repellent surface and would find application in suspensions. Dispersing agents cause breakdown of aggregates or floccules and are often added to suspensions and dispersions; in most cases, one surfactant serves both as a wetting and dispersing agent. Emulsifying agents stabilize the dispersion of one liquid in another where the two are immiscible such as in the preparation of intravenous fat emulsions. Solubilizing agents aid in dissolving small quantities of substances which would not normally be soluble. Surfactants have also been used to control the particle size of insoluble materials and also as preservatives against bacterial contamination.

The term "protective colloid" is frequently encountered in conjunction with surfactants since it is used to describe substances that assist in stabilizing suspensions against coagulation or flocculation. The distinction between one substance that is designated as a protective colloid and another that is considered a wetting agent is not to be sharply drawn. Protective colloids of the type of soluble gums (gum arabic, tragacanth) proteins (gelatin, casein, albumin) glucosides (saponin) ordinarily show only a small reduction in surface tension of water and are moreover used in relatively large concentrations. Many surface active agents on the other hand are markedly effective in lowering the surface tension of water when added in very small quantities. This paper is restricted to comments on the latter class of compounds.

Insufficient data prevent quantitative correlation between chemical structure, surface active behavior, and toxicity in surface active agents. This re-emphasizes the fact that for each individual use

attention should be placed on that toxicological behavior which most nearly parallels that use. The general structural characteristics of surface active molecules are quite well-known. For any given compound to display surface activity, there must be present in the molecule a hydrophobic (water repelling) hydrocarbon portion to which is attached one or more hydrophilic (water loving) groups. These compounds are classified as anionic or cationic depending upon whether the hydrocarbon portion of the molecule acquires a negative or positive charge upon ionization. In addition to these two, there is a third category; namely, non-ionic surface active compounds, which possess water solubility by virtue of the multiplication of weakly hydrophilic groups in the molecule. The anionic types embrace the ordinary soaps and are recognized for the most part as detergents. The cationic type compounds are quite stable with some members exhibiting powerful bactericidal properties. The non-ionic compounds possess certain advantages due to the absence of ionic groups and their effectiveness over a wide pH range. While anionics and cationics have limited application in parenterals, the non-ionics, because of lesser toxicity, have wider use.

The anionic surface active agents have not been used much in parenteral formulations. One, sodium morrhuate, is official in the USP XV. It is used in 5% solution as a sclerosing agent (5). The limited uses of this class of surfactants is undoubtedly due to the irritating and hemolytic action exerted by these compounds. Although some cationic and non-ionic surface active agents also cause hemolysis, the anionic compounds do so at very low concentrations. Recently, the kinetics of hemolysis of red blood cells by synthetic surfactants have been described in an attempt to explain the mechanism by which hemolytic agents act (6, 7). Sodium lauryl sulfate, official in the USP XV, and a typical example of the anionic type, was included in this study. This material was found to cause 100% rapid lysis in concentrations of about .004%. This amount of hemolysis would be unacceptable physiologically. The USP, therefore, cautions that sodium lauryl sulfate is intended for external use only.

A number of anionic surface agents have been studied for their bactericidal properties (8-12) and only one or two members showed some activity. The anionic types generally are not as effective bactericidally as the cationic surfactants. The largest application in

pharmacy for anionic surface active agents probably remains for topical use.

Like the anionics, the cationic surface active agents have had limited application in parenteral formulations. The cationic or quaternary ammonium compounds are peculiar in that they are used principally for their germicidal action and only secondarily for their detergent effect. They are by far, the most toxic of the surface active agents and require careful studies in order to assess long-term effects of chronic exposure. Lehman (13) tested thirteen quaternary ammonium surfactants for acute and chronic toxicity and noted that results after administration to animals ranged from changes in the gastro-intestinal tract to ganglionic blocking action. Another report (14) stated that the biological effect was the inhibition of cholinesterase.

A very thorough review of the history, chemistry, biology, and application of the quaternary ammonium salts has been compiled by Lawrence (3). This text also notes the absence of pharmacological and toxicological data of most quaternary ammonium germicides on the market. Three compounds, however, have been studied rather comprehensively; these are benzalkonium chloride (15, 16), myristyl-gamma-picolinium chloride (17), and cetyl pyridinium chloride (18). Their comparative toxicities are shown in Table I.

TABLE I

SOME TOXICITIES OF THREE CATIONIC SURFACTANTS

	I.V. LD_{50} Rats	*Oral LD_{50} Rats*	*Rabbit Eye Irritation*
Cetyl pyridinium chloride	30 mg./Kg.	200 mg./Kg.	1-5000 slightly irritating
Myristyl-γ-picolinium chloride	30 mg./Kg.	250 mg./Kg.	1-3000 slightly irritating
Benzalkonium chloride		350 mg./Kg.	1-5000 little irritation

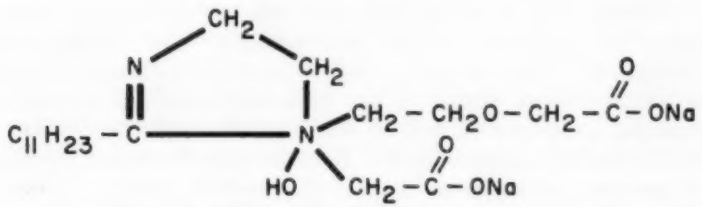
Although the use of cationic surface active agents in parenterals has been limited, they have been used as preservatives in nasal and ophthalmic preparations. Since ophthalmic formulations are required to be sterile, their development and production fall into the Sterile Areas, and their mention here is appropriate. Both cationic and

anionic surface agents in solutions or suspensions should be observed for possible incompatibility with other highly ionizable substances carrying an opposite charge.

In our laboratories, we have had occasion to test a new commercially available surface active agent described as lauroylcycloimidinium-1-ethoxy-ethionic acid-2-ethionic acid known as Miranol C2M ®[1]. This material is available as a 20% solution at pH 8.1-8.3.

FIG. 1

STRUCTURE OF MIRANOL C2M



MIRANOL C 2M

1% SOLN. I.V. LD_{50} MICE – 221 mg./kg.

5% SOLN. I.V. LD_{50} MICE – 194 mg./kg.

10% SOLN. ORAL LD_{50} MICE – 4390 mg./kg.

CAUSES HEMOLYSIS IN CONC. > 0.018 gamma/ml.

This compound is amphoteric and embraces properties of either an anionic or cationic surfactant depending upon the pH of the solution. The information available on this compound described it as non-irritating and recommended it for skin and eye use. Toxicity tests were conducted with the following results. I.V. LD_{50} in mice was found to be 221 mg./Kg. and 194 mg./Kg. for the 1% and 5%

[1] Miranol Chemical Company, Irvington, New Jersey.

concentrations respectively. The acute oral LD_{50} of a 10% concentration was 4390 mg./Kg. The intramuscular irritation studies indicated that concentrations above 5% produced severe irritation and the same strength produced a "blinking" reaction when tested by the Draize method in the rabbit eye. Hemolysis studies using dog erythrocytes showed that Miranol C2M produced hemolysis in concentrations above 0.018 mcg/ml. In view of the results of the toxicological studies, Miranol C2M was considered a poor pharmaceutical ingredient in the concentrations tested. This very brief resumé is mentioned here to illustrate the need for detailed toxicological testing on any surface active agent whose safety is unknown.

Of the three classes of surfactants, the non-ionic surface active agents are the least toxic and most commonly used in parenteral formulations. They have been used as dispersing and wetting agents in suspensions of antibiotics and adrenocorticosteroids for intramuscular administration and as solubilizers and stabilizers in solutions of various medicinal agents. It should again be pointed out that all non-ionic surfactants are not free of undesirable toxicity. A comparative study of various non-ionic surfactants was conducted in our laboratories which indicated that some were too toxic for parenteral formulations. The results of this study are shown in Table II.

TABLE II

ACUTE TOXICITY AND HEMOLYTIC ACTIVITY OF SOME SOLUBILIZERS

Compound	I.V. LD_{50} mice of 7% solutions	Hemolysis at % Conc. 7	3.5	1.75	0.87	0.44
PEG 600						
Mono laurate[2]	8.5 ml./Kg.	++++	++++	++++	++++	++++
Myrj 52[3]	36.7 ml./Kg.	+++	+	—	—	—
Brij 35[3]	13.0 ml./Kg.	+	—	—	—	—
Tween 40[3]	>50.0 ml./Kg.	+++	+	—	—	—
Antarox A 200[4]	1.2 ml./Kg.	++++	++++	++++	++++	++++
PEG 1000						
Monooleate[2]	18.4 ml./Kg.	++++	++++	++++	++++	++++
Myrj 49[3]	10.2 ml./Kg.	++++	+++	+	—	—

[2] Kessler Chemical Company, Philadelphia, Pa.
[3] Atlas Powder Company, Wilmington, Delaware.
[4] Antara Chemicals, Division General Dyestuff Corp., New York.
[5] Wyandotte Chemicals Corp., Wyandotte, Michigan.

In the non-ionic class, members of the polysorbate series or Tweens ®[3] and the polyoxyethylene oxypropylene Pluronic ®[5] compounds have been used in parenteral formulations.

Tweens are esters of the common fatty acids (lauric, palmitic, stearic, and oleic) and hexitol anhydrides to which have been added polyethylene chains to the non-esterified hydroxyls. The Tweens are supplied in 97-100% concentration and are virtually neutral. They are non-volatile and heat stabile. Solutions of Tweens turn cloudy upon autoclaving, but clear up upon cooling. They range from thin liquids through viscous oils to soft and hard waxes. Their solubility ranges from water to oil.

Pluronic F-68 has a molecular weight of about 7500, is practically tasteless, and is the largest molecule in the Pluronics series. It is offered in the flake form; whereas, other lower molecular weight Pluronics are light yellow liquids. The Pluronics have the reverse solubility properties characteristic of non-ionics. The F-68 is so soluble it shows no cloud point in distilled water even at the boiling point.

The next table indicates the rather low order of toxicity of two members of this series (19, 20).

TABLE III

TOXICITY OF TWEEN 80 AND PLURONIC F-68

	LD_{50} Oral Rats	*LD_{50} I.V. Rats*
Tween 80	>25 Gm./Kg.	5.8 Gm./Kg.
Pluronic F-68	>15 Gm./Kg.	7.7 Gm./Kg.

A microcrystalline suspension of desoxycorticosterone trimethylacetate containing 0.1% polyoxyethylene sorbitan monolaurate (Tween 20®) has been used clinically (21) as well as a suspension of hydrocortisone acetate which contains about 0.4% of the monooleate derivative (22). In these preparations, the surfactant serves as a dispersing and wetting agent, and the suspensions are administered intramuscularly or intra-articularly. While the suspensions containing these wetting agents appear to be well tolerated by man, Goth and his co-workers (23) as well as Krantz and his associates (20) observed a depressor response when Tween 20 and Tween 80 were administered intravenously to dogs. The depressor response was caused by the liberation of a histamine-like substance. Krantz *et al.*

(24), however, found that these Tweens did not illicit a histamine response in man. Goth, on the other hand, observed that cortisone inhibited this same reaction in dogs. Krantz also noted that Tween 20 was an effective hemolytic agent when tested in vitro at levels of 0.1%; other Tweens, however, exhibited less hemolytic activity. Thus, while Tween 20 is not an attractive candidate for intravenous preparations, another member, the monostearate or Tween 60 compound, has been evaluated as an emulsifying agent in intravenous fat emulsions (25, 26). Schmidt *et al.* (27) administered 0.5% Tween 60 in 5% dextrose to human volunteers and found the compound was well tolerated. On the basis of these studies, emulsions of 10% vegetable oil prepared with 0.5% Tween 60 were administered first to animals and then to human volunteers and patients. In the human trials, administration of the emulsion caused side effects which consisted of flushing of the face, epigastric or substernal distress and cough after only a few ml. were administered. In an independent study, Lambert and his co-workers (28) also found that Tween 60 stabilized emulsions were unsuitable for use in the human. The toxic results obtained with these emulsions but not observed in the I.V. administration of Tween 60 solution was not explained.

Polyoxyethylene sorbitan monooleate has been suggested as a solubilizer for reserpine (29) and the safety of such a combination would of course have to be established by animal and clinical tests, especially if the preparation is to be used intravenously. An unexpected result was encountered by Dam and his associates (30) who used Tween 80 to prepare colloidal solutions of vitamin K_1. These workers found that intravenous administration of their preparation caused pulmonary granuloma which they attributed to their stabilizer Tween 80.

Another non-ionic surface active agent, a polyoxyethylene polymer known as Pluronic F-68, has been evaluated clinically as an emulsifying agent for fat emulsions (19). This surfactant was used in a 15% cottonseed oil emulsion containing 1.2% phosphatides, 0.3% Pluronic F-68, and 4% dextrose. The toxicity data obtained on Pluronic F-68 indicated it has a wide safety margin for use. It was found, however, that the soybean phosphatides in the emulsion stimulate the liberation of a heparin-like substance which prolonged the clotting time when administered intravenously (31, 32). Although this property may be undesirable for intravenous injection, it has not

prevented the use of lecithin in penicillin suspensions intended for intramuscular administration.

The use of non-ionic surface active agents in formulations which would also include preservatives necessitates some mention of the studies of Tice and Barr (33) indicating complex formation between preservatives containing phenolic OH groups and those surfactants with polyether groups. The study showed that solutions containing Tweens could be effectively preserved by sorbic acid, the phenylmercuric salts, or benzalkonium chloride to mention a few. Sterility and effective preservation of parenteral preparations is, of course, of utmost importance.

In conclusion, it can be stated that a few surfactants have been used clinically in parenteral formulations although the non-ionic surface active agents hold most promise. However, in all cases, complete toxicological studies should be conducted to ascertain safety of any parenteral or ophthalmic preparation containing a surface active agent.

Acknowledgment

The author wishes to thank Mr. S. E. McKinney and Mr. J. A. Duddy for some of the pharmacological data as well as Dr. A. Marcus and Mr. R. Stauffer for their cooperation in making available some of the data.

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CHEMOTHERAPEUTIC MANAGEMENT OF MONOCYTIC LEUKEMIA

By John R. Sampey *

MONOCYTIC leukemia shows some striking differences from other types of leukemia in its response to chemotherapy. 6-Mercaptopurine and folic acid antagonists are the agents of first and second choice in the chemotherapeutic control of monocytic leukemia. Neither of these rates among the most used chemicals in the management of lymphocytic, myelocytic, or granulocytic leukemia.[1] Myleran is the agent of first choice in each of these three common types of leukemia, but only one investigator attributed partial remissions in three cases of monocytic leukemia on myleran therapy. Nitrogen mustard, however, is the third most frequently employed chemical in monocytic, lymphocytic, and myelocytic leukemia.

Table I lists the response of 257 patients with monocytic leukemia to chemotherapy.

TABLE I

CHEMOTHERAPEUTIC CONTROL OF MONOCYTIC LEUKEMIA

Chemicals	*No. of Cases*	*No. of Remissions*		*No. of References*
		Good	*Fair*	
6-MP	64	16	11	16
FAA	50	5	18	14
ACTH/Cortisone	31	4	5	21
N-mustards	45	7	5	11
TEM	33	4	8	8
Miscellaneous	34	6	10	11

In this tabulation of investigations published since 1949, only 18 cases were identified as chronic monocytic and 125 as acute monocytic leukemia. The five chemical agents listed account for 87% of the patients treated. The number of patients treated and responding is

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[1] Sampey, J. R., *Am. J. Surg. 95,* 970-3 (1958); *J. So. Car. Med. Assoc. 54,* 53 (1958); *ibid. 54,* 242-4 (1958).

too limited for statistical evaluation, but 6-MP and TEM give the highest remission rates, calculated from reports which give both the number on therapy and the number responding. The response of monocytic leukemia patients to all chemical agents is seen to be less than that of myelocytic and lymphocytic.

6-MP. One-fourth of the patients listed in Table I were given 6-mercaptopurine therapy. Sixteen good and 11 fair remissions in 64 patients is in line with the remission rate of this chemical in other types of leukemia even though other chemicals have been tried earlier and more frequently on the more common types of these blood diseases. Good remissions lasting for 6 months have been described with 6-MP, and few undesirable reactions have been noted.

FAA and/or ACTH/Cortisone. These three agents are frequently combined in the therapy of various leukemias. Table I shows that one-fifth of the patients listed were managed with folic acid antagonists (FAA): five good and 18 fair responses was a better showing than 4 good and 5 fair in 31 on ACTH/cortisone. Fessas reported ACTH/cortisone therapy was contraindicated in one case.

N-Mustard and TEM. Almost one-third of the patients in this review of monocytic leukemia were treated with nitrogen mustards or triethylene melamine. TEM showed the higher remission rate with 12 responses in 33 cases, but N-mustards had 7 good remissions to 4 for TEM. HN2, rather than the newer N-mustards, has been employed, although DeVries reported no response with CB1348, and Bouroncle noted one good and one fair remission in 10 patients with this same derivative.

Miscellaneous Chemicals. The score of investigations describing the use of miscellaneous chemicals in the control of monocytic leukemia make interesting reading. Five of these give trials with radiophosphorus. Cooper reported no change in 3 acute cases but one, chronic, had a 7 months' remission. Fauvert noted one in 3 chronic cases responded to P^{32}, and Mallarme reported a partial response with chronic monocytic leukemia. Guerin employed x-rays and P^{32} in one case, and Wintrobe listed this isotope as contraindicated in acute cases.

Petrakis described partial remissions in 3 patients with monocytic leukemia on myleran therapy, but Kurrle found it ineffective

in 2 cases, although with chronic myeloid leukemia he rated myleran better than TEM or urethan. Wintrobe listed myleran as ineffective in acute monocytic leukemia.

Anglesio and Garbato noted one good remission each with urethan therapy on chronic monocytic leukemia, but Dustin concluded this agent gave doubtful results in 2 acute cases. In 1955, Mayall described good tolerance and marked improvement in one chronic monocytic leukemia on colcemid treatment and, the next year, he recorded 3 more partial remissions with colchicines.

Shay obtained one partial remission in 3 chronic cases with thio-TEPA, and Marmont described a hematic remission in one monocytic leukemia with granulocytopenia induced by TEM. Marlow recorded no effect of glucosamine in one case of acute monocytic leukemia, and Weisberger noted negative results in one chronic case treated with selenium cystine.

Acknowledgments

The original literature has been made available for this study by the National Library of Medicine and the libraries of Furman University and the Greenville General Hospital.

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SELECTED ABSTRACTS

The Percutaneous Absorption of Drugs. Gemmell, D. H. O., and Morrison, J. C. *J. Pharm. and Pharmacol. 10:*553 (1958). The percutaneous absorption of salicylic acid, sulfanilamide, copper acetylacetonate, and copper sulfate from the three bases, lard, emulsifying ointment B. P., and water in the form of a five per cent carboxymethyl cellulose solution was compared. Each compound was applied to the skin of rabbits and the absorption evaluated on the basis of the blood level obtained.

The authors concluded that the physico-chemical nature of the drug was of the greatest importance in dictating the absorption through the skin. Salicylic acid showed the highest absorption from all three bases. Salicylic acid is lipid soluble. It has been postulated that the final barrier to the dermal blood supply is lipoid in nature. Therefore, if the mechanism of absorption depends on the partitioning of the drug across this barrier, drugs which are lipid soluble, such as salicylic acid, will be absorbed more rapidly than those which are lipid insoluble. Further substantiating this theory was the fact that copper sulfate, the drug having the highest water solubility but the lowest lipid solubility, was absorbed the least.

Differences in absorption of the drugs from the different bases was surprisingly small. However, with each drug, the best absorption was obtained from lard; next best, from emulsifying ointment B. P.; and the least absorption from water, in the form of a five per cent carboxymethyl cellulose solution. If it is true that the final barrier to the dermal blood supply is lipoid in nature, greater absorption would be expected from an oil phase vehicle miscible with the skin glycerides and fatty acids. The low levels of absorption from water further support this view.

The concentration of the drug first used in the bases was 10 per cent weight in weight. However, the salicylic acid concentration was lowered to 5 per cent in order to reduce the local irritant and keratolytic effect.

The Treatment of Trichuriasis With Dithiazanine. Swartzwelder, J. C. *Am. J. Trop. Med. and Hygiene 7:329* (1958). The treatment of whipworm infestations (trichuriasis) with dithiazanine (Delvex) proved to be quite successful in over 400 adults and children. In one instance, mass therapy of 262 individuals in an institution for the mentally retarded, resulted in a clinical cure rate up to 100 per cent after 10 days of therapy and a reduction in the total egg count also of 100 per cent after 10 days of therapy. In a trial with 36 children, complete clinical cures were obtained. The diarrhea or dysentery terminated and the total egg count was reduced 98.2 per cent.

The drug also proved to be effective against *Ascaris lumbricoides* infestations. In one group of 37 patients with ascariasis, there was a 96.2 per cent reduction in the total egg count and a complete parasitic cure in 65 per cent of the cases, after 5 to 10 days of treatment. These results were considered to be particularly significant since the treatment was directed against trichuriasis and since trichuriasis and ascariasis frequently occur as mixed infestations in endemic areas.

No serious untoward reactions were observed in patients in doses of 20 mg. per lb. up to a maximum of 600 mg. a day in three divided doses. Treatment periods varied from 1 to 21 days.

BOOK REVIEWS

Solvent Extraction in Analytical Chemistry. George H. Morrison and Henry Freiser. 269 pp. John Wiley & Sons, Inc., New York, N. Y., 1957.

The first part of this book is devoted to the general principles of solvent extraction as they apply to the extraction of metals. Metal extraction systems are classified into coordination (chelate) extraction systems and ion association extraction systems. A theory is developed and discussed which is applied to the many diverse metal extractions frequently used. Chapters on the formation of metal complexes, distribution, chemical interactions, quantitative treatment of equilibria, and kinetics of extraction are included.

Part Two of the book is devoted to the apparatus and techniques of solvent extraction as a separation method. Based on the considerable experience of the authors, this section should prove especially useful to the practicing chemist.

Part Three is a valuable survey of extraction systems. This is arranged under two headings; the first, "Ion Association Systems", contains a survey of fifteen different types of such extraction systems, and touches briefly on several others. The second heading, "Chelate Systems", contains a detailed discussion of fifteen metal chelating agents, and mentions several others briefly.

In Part Four are presented selected methods of extraction for the elements. The coverage is excellent; one or more methods are described for the extraction of 66 elements. Interfering elements are pointed out; references are provided.

An Appendix, listing the physical constants of organic solvents is included, followed by an index of extraction methods of the elements and, finally, a general index.

As pointed out by the authors, solvent extraction has only recently achieved recognition as an important separation technique. This book is an attempt to bring together for the first time in one place a comprehensive treatment of the principles and the practical aspects of this important field.

LOUIS A. REBER

Methoden der Organischen Chemie (Houben-Weyl). Volume 1, Part 1. Allgemeine Laboratoriumspraxis. Edited by Eugen Müller. 1048 pages, with 517 illustrations. Georg Thieme Verlag, Stuttgart, 1958. DM 198 (approximately $46).

The first part of this volume, comprising 120 pages in 8 chapters, is devoted to a discussion of the forms and properties of various materials used in laboratories, these including different types of glasses, stoppers and other closures, ceramic materials, metals used in laboratory technology, elastomers, adhesive and sealing compounds, and laboratory clamps, stands, and supports.

The second part, of 825 pages, consists of 21 chapters on theory and procedures for preparative separation, isolation, and purification of organic compounds. Chapter titles are as follows: (1) Decantation, Filtration, and Ultrafiltration (43 pages); (2) Washing, Clarification and Decoloration (18 pages); (3) Expression (12 pages); (4) Breaking of Emulsions (13 pages); (5) Distribution and Extraction (114 pages); (6) Crystallization (49 pages); (7) Preparation and Separation of Inclusion Compounds (26 pages); (8) Isolation of Substances through Formation of Complex and Double Compounds (36 pages); (9) Salting-out (12 pages); (10) Isolation, Purification and Separation through Adsorption in the Liquid State (28 pages); (11) Isolation, Purification and Separation through Adsorption from the Gaseous State (but not including gas chromatography) (28 pages); (12) Ion Exchange (80 pages); (13) Redox Processes (18 pages); (14) Centrifugation (34 pages); (15) Dialysis and Electrodialysis (28 pages); (16) Preparative Electrophoresis (72 pages); (17) Drying of Stable Substances (24 pages); (18) Distillation and Rectification (112 pages); (19) Evaporation (8 pages); (20) Distillation and Sublimation under Moderate and High Vacuum (including Freeze-Drying) (60 pages); (21) References on Planning and Arrangement of Organic Chemistry Laboratories (2 pages).

This volume of Houben-Weyl should be useful not only to the organic chemists to whom it is directed, but also to all other chemists concerned with the subjects described.

ARTHUR OSOL

Introduction to Protein Chemistry. S. W. Fox and J. F. Foster. viii + 459 pp. John Wiley & Sons, Inc., New York 16, N. Y., 1957. Price $9.50.

This book is intended to be used as a text in conjunction with a course on protein chemistry. As the title indicates, it is necessarily an introductory work giving the reader or student sufficient basic information and enough references to pursue the topic more completely. The twenty-four chapters discuss the amino acids, peptides, protein systems, and enzymes as the properties, structure, preparation, purification, assay, and other important basic aspects of protein chemistry. A good balance between the chemical and physical-biological properties of the proteins should appeal to other than chemists interested in this field.

Each chapter contains an adequate supply of references at the conclusion, but it is often time-consuming to relate a particular topic in the text to a specific reference at the end of a chapter since the references are arranged in chronological order only.

The reader will find that the book reads very smoothly and it should easily fulfill the authors' aim in directing the text toward the student of protein chemistry.

A. R. GENNARO

Thiopentone and Other Thiobarbiturates. J. W. Dundee. viii + 312 pp. The Williams and Wilkins Co., Baltimore, Md., 1956.

This book is an extensive review of the various medical uses of the thiobarbiturates, especially thiopentone (Thiopental). The chemistry, properties, distribution in the body, response variations, hazards, and administration are also included. Two chapters are involved with newer thiobarbiturates and analeptics and other stimulants. The appendix contains many fine plates illustrating the apparatus used for administration and also discusses compatabilities, detection and estimation, and a few case histories.

A. R. GENNARO

Biochemical Disorders in Human Disease. Edited by R. H. S. Thompson and E. J. King. 843 pp. Academic Press, Inc., New York, N. Y., 1957. Price: $12.60.

The two author-editors, assisted by twenty-eight other contributors, have ably assembled and interpreted disorders underlying or associated with human disease. There are twenty chapters in which are considered: the gastro-intestinal tract, liver and biliary tract, anemias, blood clotting mechanisms, hypertension, kidney and genito-urinary tract, adrenals, muscle, bone, parathyroid, nervous system, reproductive organs, iodine metabolism, and metabolic disorders.

The subjects are dealt with on an "organic basis" rather than by specific disorders and, as such, present a most comprehensive understanding of how biochemistry impinges on medicine and surgery. The book not only discusses the pathogenesis of disease but the application of biochemistry in the diagnosis and management.

This is by far one of the finest compendiums to have been made available to the biochemist.

BERNARD WITLIN

Chemical Transformations by Microorganisms. Frank H. Stodola. 134 pages. John Wiley & Sons, Inc., New York, N. Y., 1957. Price: $4.25.

This is the second series of published E. R. Squibb Lectures on Microbial Products presented at the Institute of Microbiology, Rutgers, the State University of New Jersey. There are three chapters and an index.

Chapter one—"The Chemical Anatomy of Microorganisms, with Special Reference to *M. tuberculosis*"—considers lipids, wax coats, polysaccharides, proteins, nucleic acids, capsules, cell walls, flagella, cytoplasmic membranes and granules.

Chapter two—"Organic Type Reactions of Microorganisms"—considers fifteen type reactions in microbiological chemistry.

Chapter three—"Synthetic Powers of Microorganisms"—considers three pigments (penitrinic acid, herqueinone, and phenazine *a*-carboxylic acid), antibiotics, acids, and the gibberellins.

This is one of the finest presentations on the biochemical role of microorganisms in research and industry.

BERNARD WITLIN

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